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=> file ca,uspatful,biosis,medline,drugu,embase

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=> s etanercept or infliximab or (TNF or tumor necro? factor or tumour necro?
factor)(3a)(receptor? or antagonist? or block? or inhibit?) or cdp571 or d2e7

   3 FILES SEARCHED...
   5 FILES SEARCHED...
L1       45274 ETANERCEPT OR INFLIXIMAB OR (TNF OR TUMOR NECRO? FACTOR OR
TUMOU
               R NECRO? FACTOR)(3A)(RECEPTOR? OR ANTAGONIST? OR BLOCK? OR
INHIB
               IT?) OR CDP571 OR D2E7

=> s retina? or (optic or ocula? or macula?)(2a)(nerve? or neuritis or
degenerat?) or retinitis or retinopath?

L2      382920 RETINA? OR (OPTIC OR OCULA? OR MACULA?)(2A)(NERVE? OR NEURITIS
               OR DEGENERAT?) OR RETINITIS OR RETINOPATH?

=> s l1 and l2

L3         387 L1 AND L2

=> s l1(l)l2

L4         313 L1(L) L2

=> s l3 and l4

L5         313 L3 AND L4
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=> dup rem l5

PROCESSING COMPLETED FOR L5
L6 257 DUP REM L5 (56 DUPLICATES REMOVED)

=> s l1(10a)l2

L7 39 L1(10A) L2

=> s l1(20a)l2

L8 60 L1(20A) L2

=> dup rem l8

PROCESSING COMPLETED FOR L8
L9 36 DUP REM L8 (24 DUPLICATES REMOVED)

=> d 1-36 bib,ab

L9 ANSWER 1 OF 36 CA COPYRIGHT 2001 ACS DUPLICATE 1
AN 134:114846 CA
TI TNF inhibitors for the treatment of neurological disorders
IN Tobinick, Edward L.
PA USA
SO U.S., 9 pp., Cont.-in-part of U.S. 6,015,557.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6177077	B1	20010123	US 1999-476643	19991231
	US 6015557	A	20000118	US 1999-275070	19990323
PRAI	US 1999-256388	B2	19990224		
	US 1999-275070	A2	19990323		

AB A method is disclosed for inhibiting the action of TNF for treating neurol. conditions in a human by administering a TNF antagonist for reducing the inflammation of neuronal tissue or the neuromuscular junction of a human, or for modulating the immune response affecting neuronal tissue or the neuromuscular junction of a human by administering to the human a therapeutically effective dosage level of a TNF antagonist. The TNF antagonist is selected from the group consisting of etanercept, infliximab, pegylated sol. TNF receptor Type I (PEGsTNF-R1), other agents contg. sol. TNF receptors, CDP571 (a humanized monoclonal anti-TNF-alpha antibody), other monoclonal anti-TNF-alpha antibodies, TNF-alpha converting enzyme inhibitors and D2E7 (a human anti-TNF mAb) for reducing the inflammation of neuronal tissue or the neuromuscular junction of a human, or for modulating the immune response affecting neuronal tissue or the neuromuscular junction of a human.
RE.CNT 6
RE
(1) Carlino; US 5650396 1997 CA
(2) Jacobs; US 5605690 1997 CA
(3) Le; US 5656271 1997 CA
(4) Levin; US 5962481 1999 CA
(5) Roberts; US 5574022 1996 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 36 CA COPYRIGHT 2001 ACS
AN 134:130275 CA
TI Promotion or inhibition of angiogenesis and cardiovascularization by tumor

necrosis factor ligand/receptor homologs
IN Williams, P. Mickey; Gerritsen, Mary E.
PA Genentech, Inc., USA
SO PCT Int. Appl., 92 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001003720	A2	20010118	WO 2000-US18867	20000711

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-143304 P 19990712
AB Compns. contg. PRO364 (hGITR) or PRO175 (hGITRL) are disclosed for stimulating or inhibiting angiogenesis and/or cardiovascularization in mammals, including humans. The compns. can comprise a further active ingredient, namely, a cardiovascular, endothelial, or angiogenic agent or an angiostatic agent. Disorders that can be diagnosed, prevented, or treated by the compns. herein include trauma such as wounds, various cancers, and disorders of the vessels including atherosclerosis and cardiac hypertrophy.

L9 ANSWER 3 OF 36 USPATFULL
AN 2001:52209 USPATFULL
TI Antisense modulation of bcl-x expression
IN Bennett, C. Frank, Carlsbad, CA, United States
Dean, Nicholas M., Olivenhain, CA, United States
Monia, Brett P., LaCosta, CA, United States
Nickoloff, Brian J., Burr Ridge, IL, United States
Zhang, QingQing, San Diego, CA, United States
PA Isis Pharmaceuticals, Inc., Carlsbad, CA, United States (U.S. corporation)
PI US 6214986 20010410
AI US 1999-323743 19990602 (9)
RLI Continuation-in-part of Ser. No. US 1999-277020, filed on 26 Mar 1999
Continuation-in-part of Ser. No. US 1998-167921, filed on 7 Oct 1998
DT Utility
EXNAM Primary Examiner: Schwartzman, Robert A.; Assistant Examiner: Epps, Janet
LREP Law Offices of Jane Massey Licata
CLMN Number of Claims: 50
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2613
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Compositions and methods are provided for modulating the expression of bcl-x. Antisense compounds, particularly antisense oligonucleotides, targeted to nucleic acids encoding bcl-x are preferred. Methods of using
these compounds for modulation of bcl-x expression and for treatment of diseases associated with expression of bcl-x are also provided. Methods of sensitizing cells to apoptotic stimuli are also provided.

L9 ANSWER 4 OF 36 MEDLINE DUPLICATE 2
AN 2001198474 MEDLINE
DN 21136903 PubMed ID: 11238868
TI Rabies virus ocular disease: T-cell-dependent protection is under the

control of signaling by the p55 tumor necrosis factor alpha receptor, p55TNFR.
AU Camelo S; Castellanos J; Lafage M; Lafon M
CS Unite de Neurovirologie et Regeneration du Systeme Nerveux, Institut Pasteur, Paris, France.
SO JOURNAL OF VIROLOGY, (2001 Apr) 75 (7) 3427-34.
Journal code: KCV; 0113724. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200104
ED Entered STN: 20010410
Last Updated on STN: 20010410
Entered PubMed: 20010312
Entered Medline: 20010405
AB Following brain infection, the Challenge Virus Standard strain of rabies virus infects the retina. Rabies virus ocular infection induces the infiltration of neutrophils and predominantly T cells into the eye. The role of tumor necrosis factor alpha (TNF-alpha)-lymphotoxin signaling in the control of rabies virus ocular infection and inflammatory cell infiltration was assessed using mice lacking the p55 **TNF**-alpha **receptor** (p55TNFR(-/-) mice). The incidence of ocular disease and the intensity of **retinal** infection were greater in p55TNFR(-/-) mice than in C57BL/6 mice: the aggravation correlated with less neutrophil
and T-cell infiltration. This indicates that cellular infiltration is under the control of the p55 TNF-alpha receptor and suggests that inflammatory cells may protect the eye against rabies virus ocular infection. The role of T cells following rabies virus ocular disease was assessed by comparison of rabies virus infection in nude mice with their normal counterparts. Indeed, the incidence and severity of the rabies virus ocular disease were higher in athymic nude mice than in BALB/c mice,
indicating that T lymphocytes are protective during rabies virus ocular infection. Moreover, few T cells and neutrophils underwent apoptosis in rabies virus-infected retina. Altogether, these data suggest that T lymphocytes and neutrophils are able to enter the eye, escape the immune privilege status, and limit rabies virus ocular disease. In conclusion, rabies virus-mediated eye disease provides a new model for studying mechanisms regulating immune privilege during viral infection.

L9 ANSWER 5 OF 36 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:183436 BIOSIS
DN PREV200100183436
TI Interphotoreceptor retinoid binding protein peptide-induced uveitis in B10.RIII mice: Characterization of disease parameters and immunomodulation.
AU Hankey, Deborah J. R. (1); Lightman, Susan L.; Baker, David
CS (1) Neuroinflammation Group, Department of Neurochemistry, Institute of Neurology, University College London, 1 Wakefield Street, London, WC1N 1PJ: dhankey@hgmp.mrc.ac.uk UK
SO Experimental Eye Research, (March, 2001) Vol. 72, No. 3, pp. 341-350. print.
ISSN: 0014-4835.
DT Article
LA English
SL English
AB Experimental autoimmune uveoretinitis (EAU) can be induced in the B10.RIII
mice following immunization with bovine interphotoreceptor retinoid binding protein (IRBP) and human IRBP161-180 peptide. This study examines the value of the human IRBP161-180 peptide model in the B10.RIII mice, as a suitable model of EAU in order to examine immunotherapies. Having established a reliable and consistent immunization protocol of 25 mug

peptide and no PTX, the time course of histopathology was performed, which graded both cellular and structural scores individually. Disease was typically of an acute nature, characterized by rapid onset of a massive inflammatory response, resulting in extensive damage to the rod outer segments (ROS) and neuronal layers. Treatment with potent immunosuppressive agents, CD4-specific monoclonal antibodies resulted in the inhibition of disease and a reduction in disease incidence. Treatment with p55-**tumor necrosis factor receptor**-Ig (p55-TNFR-Ig) fusion protein reduced structural damage to the **retina** despite a high level of cellular infiltration in the eye, suggesting that target organ damage in an acute model of EAU can be modulated.

L9 ANSWER 6 OF 36 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 3
AN 2001:148656 BIOSIS
DN PREV200100148656
TI Dexamethasone alters TNF-alpha expression in retinopathy.
AU Yossuck, Panitan; Tadesse, Yun Yan Misrak; Higgins, Rosemary D. (1)
CS (1) Department of Pediatrics, Division of Neonatology, Georgetown University Children's Medical Center, 3800 Reservoir Road, NW, Room M3400, Washington, DC, 20007: higginsr1@gunet.georgetown.edu USA
SO Molecular Genetics and Metabolism, (February, 2001) Vol. 72, No. 2, pp. 164-167. print.
ISSN: 1096-7192.
DT Article
LA English
SL English
AB TNF-alpha has been found in the **retina**. Hyperoxia and hypoxia regulate TNF-alpha expression. TNF-alpha is an important factor in inflammation and angiogenesis. Dexamethasone **inhibits TNF**-alpha production. Changes in TNF-alpha expression in the **retina** may play an important role in the development of oxygen-induced retinopathy. Oxygen-induced retinopathy was produced in C57BL6 mice by exposure to 75% oxygen at Postnatal Day 7 (P7) for 5 days and the mice recovered in room air until Day 17 (P17). Dexamethasone was administered at 0.5 mg/kg/day once daily subcutaneously during the 5 days of oxygen exposure. TNF-alpha expression was evaluated at Day 7 prior to oxygen exposure, at Day 12 (P12) immediately upon removal from oxygen, and at Day 17, the time of maximal vasoproliferation by RT-PCR. TNF-alpha is developmentally regulated in the retinae of C57BL6 mice. From P7 to P12, there is a 3-fold increase in TNF-alpha expression and from P7 to P17 there is a 2.7-fold increase. There was 2.7-fold suppression in expression immediately following oxygen exposure at P12. The expression was dramatically increased at P17, the time of maximal vasoproliferation. Dexamethasone inhibited the expression of TNF-alpha at P17 by 6.4-fold. At this dose, it also suppressed the baseline TNF-alpha expression in the mouse model. In summary, TNF-alpha is altered in the development of oxygen-induced retinopathy in the mouse. It increased markedly during the vasoproliferative phase and was suppressed by dexamethasone. Modulation of TNF-alpha expression may provide a potential site of action for future therapeutic targets.

L9 ANSWER 7 OF 36 USPATFULL
AN 2000:7079 USPATFULL
TI Trapidil for use in the therapy of syndrome that may be influenced by immunomodulators
IN Walch, Hatto, Laupheim, Germany, Federal Republic of
PA Rodleben Pharma GmbH, Rodleben, Germany, Federal Republic of (non-U.S. corporation)

PI US 6015578 20000118
WO 9632111 19961017
AI US 1997-945216 19971009 (8)
WO 1996-EP1037 19960311
19971009 PCT 371 date
19971009 PCT 102(e) date
PRAI DE 1995-19514048 19950413
DT Utility
EXNAM Primary Examiner: Page, Thurman K.; Assistant Examiner: Benston, Jr., William Edward
LREP Ratner & Prestia
CLMN Number of Claims: 19
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 395
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Trapidil is used in the therapy of syndromes that may be influenced by immunomodulators. Trapidil is used for the preparation of a drug for the
therapy or prophylaxis of diseases associated with TNF-induced pathological disorders.

L9 ANSWER 8 OF 36 USPATFULL
AN 2000:7059 USPATFULL
TI Tumor necrosis factor antagonists for the treatment of neurological disorders
IN Tobinick, Edward L., 100 UCLA Medical Plz., Suite 205, Los Angeles, CA, United States 90024-6903
Tobinick, Arthur Jerome, 100 UCLA Medical Plz., Suite 205, Los Angeles, CA, United States 90024-6903
PI US 6015557 20000118
AI US 1999-275070 19990323 (9)
RLI Continuation-in-part of Ser. No. US 1999-256388, filed on 24 Feb 1999, now abandoned
DT Utility
EXNAM Primary Examiner: Jarvis, William R. A.
LREP Sutton, Ezra
CLMN Number of Claims: 47
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 710
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method for inhibiting the action of TNF for treating neurological conditions in a human by administering a TNF antagonist for reducing damage to neuronal tissue or for modulating the immune response affecting neuronal tissue of the human. The TNF antagonist administered is selected from the group consisting of etanercept and infliximab. The TNF antagonist is administered subcutaneously, intravenously, intrathecally, or intramuscularly.

Methotrexate or Leflunomide may be administered concurrently with the TNF antagonist for demyelinating diseases and certain other neurological
disorders.

L9 ANSWER 9 OF 36 MEDLINE DUPLICATE 4
AN 2001106663 MEDLINE
DN 20556628 PubMed ID: 11102475
TI Increased production of tumor necrosis factor-alpha by glial cells exposed
to simulated ischemia or elevated hydrostatic pressure induces apoptosis in cocultured retinal ganglion cells.
AU Tezel G; Wax M B
CS Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, St. Louis, Missouri 63110, USA.

NC EY12314 (NEI)
SO J Neurosci, (2000 Dec 1) 20 (23) 8693-700.
Journal code: DO0. ISSN: 1529-2401.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200102
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered PubMed: 20010104
Entered Medline: 20010208
AB Although glial cells in the optic nerve head undergo a reactivation process in glaucoma, the role of glial cells during glaucomatous neurodegeneration of retinal ganglion cells is unknown. Using a coculture system in which retinal ganglion cells and glial cells are grown on different layers but share the same culture medium, we studied the influences of glial cells on survival of retinal ganglion cells after exposure to different stress conditions typified by simulated ischemia and elevated hydrostatic pressure. After the exposure to these stressors, we observed that glial cells secreted tumor necrosis factor-alpha (TNF-alpha) as well as other noxious agents such as nitric oxide into the coculture media and facilitated the apoptotic death of retinal ganglion cells as assessed by morphology, terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling, and caspase activity. The glial origin of these noxious effects was confirmed by passive transfer experiments. Furthermore, retinal ganglion cell apoptosis was attenuated approximately 66% by a neutralizing antibody against TNF-alpha and 50% by a selective inhibitor of inducible nitric oxide synthase (1400W). Because elevated intraocular pressure and ischemia are two prominent stress factors identified in the eyes of patients with glaucoma, these findings reveal a novel glia-initiated pathogenic mechanism for **retinal** ganglion cell death in glaucoma. In addition, these findings suggest that the **inhibition** of **TNF**-alpha that is released by reactivated glial cells may provide a novel therapeutic target for neuroprotection in the treatment of glaucomatous optic neuropathy.

L9 ANSWER 10 OF 36 CA COPYRIGHT 2001 ACS DUPLICATE 5
AN 133:294794 CA
TI Matrix metalloproteinases and tumor necrosis factor .alpha. in glaucomatous optic nerve head
AU Yan, Xiaoming; Tezel, Gulgun; Wax, Martin B.; Edward, Deepak P.
CS Departments of Ophthalmology and Visual Sciences, University of Illinois, Chicago, IL, USA
SO Arch. Ophthalmol. (Chicago) (2000), 118(5), 666-673
CODEN: AROPAW; ISSN: 0003-9950
PB American Medical Association
DT Journal
LA English
AB Objective: To study expression and location of matrix metalloproteinases (MMPs) and tumor necrosis factor .alpha. (TNF-.alpha.) in glaucomatous optic nerve heads, which are known to be secreted in response to a variety of neuronal injury. Methods: Four postmortem eyes from patients with primary open-angle glaucoma, 7 eyes from patients with normal-pressure glaucoma, and 4 eyes from age-matched normal donors were studied by immunohistochem. The sections of the **optic nerve** heads were examd. after immunostaining with antibodies to MMPs (MMP-1, MMP-2, and MMP-3), TNF-.alpha., or **TNF**-.alpha. **receptor** 1. Results: The intensity of the immunostaining and the no. of stained cells for MMPs, TNF-.alpha., or **TNF**-.alpha. **receptor** 1 were greater in the glaucomatous **optic nerve** heads, particularly in eyes with normal-pressure glaucoma compared with

age-matched controls. Pos. immunostaining was obsd. in all regions of the glaucomatous optic nerve heads, but most prominently in the postlaminar region. Immunostaining was obsd. mainly in glial cells and their processes around the axons and blood vessels and in pial septae. Conclusion: There is increased immunostaining for MMPs, TNF-.alpha. and **TNF**-.alpha. **receptor** 1 in the glaucomatous **optic nerve** head, which suggests increased expression of these proteins in glaucoma and thereby implies a role in the tissue remodeling and degenerative changes seen in glaucomatous optic nerve heads. Clin. Relevance: The MMPs and TNF-.alpha. may be components of astroglial activation that occurs in glaucomatous optic nerve heads. The biol. alterations in the expression of these proteins may play a role in the progression of glaucomatous optic neuropathy.

RE.CNT 44

RE

(1) Apodaca, G; Cancer Res 1990, V50, P2322 CA
(2) Backstrom, J; J Neurochem 1992, V58, P983 CA
(3) Barone, F; Stroke 1997, V28, P1233 CA
(5) Eddleston, M; Neuroscience 1993, V54, P15 CA
(7) Giraudon, P; Prog Neurobiol 1996, V49, P169 CA

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 36 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:217054 BIOSIS
DN PREV200100217054
TI Neurodegenerative and neuroprotective effects of tumor necrosis factor in **retinal** ischemia: Opposite roles of **TNF receptor** 1 and **TNF receptor** 2.
AU Eisel, U. L. M. (1); Fontaine, V. (1); Hanoteau, N.; Sahel, J.; Pfizenmaier, K. (1)
CS (1) Institute of Cell Biology and Immunology, University of Stuttgart, Stuttgart Germany
SO Immunobiology, (November, 2000) Vol. 203, No. 1-2, pp. 493. print. Meeting Info.: Joint Annual Meeting of the German and Dutch Societies of Immunology Duseldorf, Germany November 29-December 02, 2000 ISSN: 0171-2985.
DT Conference
LA English
SL English

L9 ANSWER 12 OF 36 MEDLINE
AN 2001028560 MEDLINE
DN 20432168 PubMed ID: 10975909
TI Tumor necrosis factor-alpha: a potentially neurodestructive cytokine produced by glia in the human glaucomatous optic nerve head.
AU Yuan L; Neufeld A H
CS Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, St. Louis, Missouri 63110, USA.
NC EY12017 (NEI)
SO GLIA, (2000 Oct) 32 (1) 42-50. Journal code: GLI. ISSN: 0894-1491.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200011
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered PubMed: 20001027
Entered Medline: 20001121
AB Tumor necrosis factor-alpha (TNF-alpha) mediates a range of cellular responses, which have potentially detrimental consequences that affect multiple cell types. To determine whether TNF-alpha contributes to glaucomatous optic neuropathy, we have studied the expression of this

cytokine and its **receptor, tumor necrosis factor receptor**-1 (**TNF**- R1), in human glaucomatous **optic nerve** heads from patients with different stages of disease using double labeling fluorescence immunohistochemistry. We have also investigated the ability of this cytokine to induce nitric oxide synthase (NOS-2) in cultured human optic nerve astrocytes by immunocytochemistry and immunoblot. Normal tissue showed constitutive expression of TNF-R1 in the vasculature of the optic nerve heads but no positive labeling for TNF-alpha. In the glaucomatous optic nerve heads, the expression of both TNF-alpha and TNF-R1 were apparently upregulated, primarily in glial fibrillary acidic protein (GFAP)-positive astrocytes, and appeared to parallel the progression of optic nerve degeneration. In eyes with severe glaucomatous damage, some HLA-DR positive microglia also contained TNF-alpha and TNF-R1. In the most severely damaged optic nerve heads, the axons of the retinal ganglion cells contained TNF-R1 and, therefore, are direct targets for neurodegeneration caused by TNF-alpha. In vitro astrocytes constitutively express TNF-R1 and TNF-alpha stimulation induces expression of NOS-2. We hypothesize that TNF-alpha contributes to the progression of optic nerve degeneration in glaucoma by both a direct effect on the axons of the retinal ganglion cells and by inducing NOS-2 in astrocytes.

L9 ANSWER 13 OF 36 CA COPYRIGHT 2001 ACS
AN 131:73570 CA
TI Preparation of azepinehydroxamates and related compounds as inhibitors of metalloproteinase and tumor necrosis factor release.
IN Russo-Rodriquez, Sandra E.; Koch, Kevin; Termin, Andreas; Hummel, Conrad
PA Amgen Inc., USA
SO PCT Int. Appl., 189 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9932451	A1	19990701	WO 1998-US27117	19981218
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 6107291	A	20000822	US 1998-213077	19981216
	AU 9919336	A1	19990712	AU 1999-19336	19981218
	EP 1040099	A1	20001004	EP 1998-964149	19981218
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRAI	US 1997-68227	P	19971219		
	US 1998-213077	A	19981216		
	WO 1998-US27117	W	19981218		

OS MARPAT 131:73570
AB Title compds. [I; V = CR8R11, CR8R11CHR12; R11, R12 = H, OR20, cycloalkyl, aryl, heteroaryl, (substituted) alkyl, alkenyl, alkynyl, etc.; R20 = H, (substituted) alkyl, alkenyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, alkanoyl, aroyl, etc.; R1 = (substituted) alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl; R2 = H, alkyl; R5-R8 = H, alkyl; R9, R10 = BA; B = bond, (substituted) alkyl, alkenyl, alkynyl, heterocyclyl, aryl, heteroaryl; A = H, halo, cyano, NO2, COR30, CO2R31, CONR32R31, OR31, etc.; R30 = (substituted) alkyl, alkenyl, alkynyl,

heterocyclyl, aryl, heteroaryl; R31 = H, R30; R32 = H, (substituted) alkyl, heterocyclyl, aryl, heteroaryl; with provisos], were prepd. Thus, cis-3-benzyl-1-(4-methoxybenzenesulfonyl)azepane-2-carboxylic acid (prepn.
given) in CH2Cl2 was treated with (COCl)2 and cat. DMF followed by stirring for 30 min.; the mixt. was added to a mixt. of NH2OH.HCl in THF/H2O/Et3N at 0.degree. to give cis-3-benzyl-1-(4-methoxybenzenesulfonyl)azepane-2-hydroxamic acid. Several I inhibited lipopolysaccharide-induced TNF-.alpha. prodn. in mice with IC50<10 .mu.M.

RE.CNT 6

RE

(1) Adir Et Cie; EP 0803505 A 1997 CA
(2) Ciba-Geigy Ag; EP 0606046 A 1994 CA
(3) Fibrogen Inc; WO 9705865 A 1997 CA
(4) Hoechst Ag; WO 9718194 A 1997 CA
(5) Pfizer Inc; WO 9633172 A 1996 CA

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 14 OF 36 CA COPYRIGHT 2001 ACS

AN 130:168663 CA

TI Preparation of peptidyl compounds having MMP and TNF inhibitory activity

IN Baxter, Andrew Douglas; Montana, John Gary

PA Chiroscience Limited, UK

SO PCT Int. Appl., 32 pp.
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9907679	A1	19990218	WO 1998-GB272	19980129
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 5955435	A	19990921	US 1997-908990	19970808
	AU 9858719	A1	19990301	AU 1998-58719	19980129
PRAI	US 1997-908990		19970808		
	GB 1996-16643		19960808		
	WO 1998-GB272		19980129		

OS MARPAT 130:168663

AB Peptidyl compds. R8SCHR10XNR11CHR1YNR4R5 [X = CO, CS; Y = CO, CS, SO, SO2;
R1 = (un)substituted aryl- or heteroarylalkyl; R4, R5 = H, alkyl; R8 = H, acyl; R10, R11 = H, (un)substituted alkyl, aryl, alkylaryl, heteroaryl, alkylheteroaryl,cycloalkyl, alkylcycloalkyl, heterocycloalkyl, alkylheterocycloalkyl] were prepd. as MMP and TNF inhibitors. Thus, (S)-[2-(acetylthio)-5-phthalimidopentanoyl]-(S)-2-naphthylalanine N-methylamide was prepd. by amidation of (S)-2-(acetylthio)-5-phthalimidopentanoic acid with Boc-2-naphthylalanine N-methylamide. The synthesized compds. were assayed for inhibition of collagenase, stromelysin, gelatinase, MMP, TNF .alpha. prodn., etc.

RE.CNT 4

RE

(1) Britisch Biotech Pharmaceuticals Ltd; WO 9519961 A 1995 CA
(2) Chiroscience Ltd; WO 9513289 A 1995 CA
(3) Chiroscience Ltd; WO 9611209 A 1996 CA
(4) Florida State University; WO 9509833 A 1995 CA

L9 ANSWER 15 OF 36 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 6

AN 1999:237556 BIOSIS

DN PREV199900237556
TI Evidence for control of tumour necrosis factor-alpha (TNF-alpha) activity by **TNF receptors** in patients with proliferative diabetic **retinopathy**.
AU Limb, G. A. (1); Soomro, H.; Janikoun, S.; Hollifield, R. D.; Shilling, J.
CS (1) Department of Pathology, Institute of Ophthalmology and Moorfields Eye Hospital, Bath Street, London, EC1V 9EL UK
SO Clinical and Experimental Immunology, (March, 1999) Vol. 115, No. 3, pp. 409-414.
ISSN: 0009-9104.
DT Article
LA English
SL English
AB TNF-alpha has been implicated in the pathogenesis of insulin- dependent diabetes mellitus (IDDM). At present there are no studies linking serum levels of soluble **TNF receptors** (sTNF-R) to the development of diabetic microvascular complications such as proliferative diabetic **retinopathy** (PDR), or to the production of TNF-alpha in these patients. We investigated serum levels of sTNF receptors (sTNF-RI and sTNF-RII) in IDDM patients with or without PDR, and related these to the in vitro production of TNF-alpha upon activation of whole blood and isolated mononuclear cells (MNC). We observed higher serum levels of sTNF-RI in IDDM patients with active (range 945-6630 pg/ml; P = 0.029) or quiescent PDR (range 1675-4970 pg/ml; P = 0.00092) than in individuals with IDDM without retinopathy (range 657-2617 pg/ml) or healthy controls (range 710-1819 pg/ml; P = 0.0092 and 0.0023, respectively). Increased serum levels of sTNF-RII were also seen in IDDM patients with active PDR (range 1749-5218 pg/ml; P = 0.034) or quiescent PDR (range 1494-5249 pg/ml; P = 0.0084) when compared with disease controls (range 1259-4210 pg/ml) or healthy subjects (range 1237-4283 pg/ml). Whole blood production of biologically active TNF-alpha was lower in PDR patients than in disease (P = 0.04) and healthy controls (P<0.005), contrasting with a higher production of TNF-alpha by lipopolysaccharide (LPS)-activated MNC from PDR patients (P = 0.013). Inhibition of TNF-alpha by TNF-R in plasma supernatants of activated blood from PDR patients was demonstrated by increase of TNF-alpha activity in the presence of anti-TNF-RI and anti-TNF-RII antibodies. These observations suggest that abnormalities in TNF-alpha production and control may operate during the development of microvascular complications of diabetes mellitus.

L9 ANSWER 16 OF 36 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1999:269034 BIOSIS
DN PREV199900269034
TI Platelet expression of **tumour necrosis factor** -alpha and **TNF-receptors** in patients with proliferative diabetic **retinopathy**.
AU Limb, G. (1); Webster, L.; Soomro, H.; Janikoun, S.; Shilling, J.
CS (1) Institute of Ophthalmology and Moorfields Eye Hospital, London UK
SO IOVS, (March 15, 1999) Vol. 40, No. 4, pp. S311.
Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology Fort Lauderdale, Florida, USA May 9-14, 1999 Association for Research in Vision and Opthalmology
.
DT Conference
LA English

L9 ANSWER 17 OF 36 CA COPYRIGHT 2001 ACS DUPLICATE 7
AN 132:249859 CA
TI Platelet expression of tumour necrosis factor-alpha (**TNF**

-.alpha.), **TNF receptors** and intercellular adhesion molecule-1 (ICAM-1) in patients with proliferative diabetic **retinopathy**

AU Limb, G. A.; Webster, L.; Soomro, H.; Janikoun, S.; Shilling, J.

CS Department of Pathology, Institute of Ophthalmology and Moorfields Eye Hospital, London, EC1V 9EL, UK

SO Clin. Exp. Immunol. (1999), 118(2), 213-218
CODEN: CEXIAL; ISSN: 0009-9104

PB Blackwell Science Ltd.

DT Journal

LA English

AB Microvascular complications of insulin-dependent diabetes mellitus (IDDM) have been strongly assocd. with platelet abnormalities, while TNF-.alpha. has been implicated in the pathogenesis of this condition. However, at present it is not clear whether human circulating platelets express TNF-.alpha. or TNF receptors (TNF-R) or whether impaired expression of these mols. and of the TNF-reactive adhesion mol. ICAM-1 may be assocd. with platelet abnormalities in patients with IDDM. On this basis we investigated the platelet expression of these mols. in patients with IDDM complicated or uncomplicated by proliferative diabetic retinopathy (PDR) and in healthy subjects. We obsd. that the proportion of platelets staining for TNF-.alpha. was significantly higher in IDDM patients with active PDR than in patients without microvascular complications (P = 0.0078), quiescent PDR (P = 0.003) or healthy subjects (P = 0.0013). Patients with active PDR also showed a higher proportion of platelets expressing TNF-RI (P = 0.0052) and TNF-RII (P = 0.015) than healthy controls or patients with quiescent PDR (P = 0.009 and 0.0006, resp.). In addn., the percentage of ICAM-1+ platelets was significantly higher in patients with active PDR than in patients with quiescent PDR (P = 0.0065) or normal subjects (P = 0.013). There was a direct correlation between platelet expression of TNF-.alpha. and that of TNF-R in PDR patients, indicating that platelet staining for TNF-.alpha. may be due to binding of this cytokine to its receptors. The results suggest that increased platelet expression of TNF-.alpha., TNF-R and ICAM-1 in IDDM patients may constitute important markers of thrombocyte abnormalities during the development of microvascular complications of diabetes mellitus.

RE.CNT 38

RE

(1) Bar, J; Thromb Haemost 1997, V78, P1255 CA
(2) Camussi, G; Eur J Biochem 1991, V202, P3 CA
(3) De Kossodo, S; Brit J Cancer 1995, V72, P1165 CA
(7) Grau, G; Eur Cytokine Netw 1993, V4, P415 CA
(11) Hussain, M; Diabetologia 1996, V39, P60 CA

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 18 OF 36 BIOSIS COPYRIGHT 2001 BIOSIS

AN 1999:229000 BIOSIS

DN PREV199900229000

TI An immunohistochemical study of **TNF**-alpha **receptors** in **optic nerves** from AIDS patients.

AU Sadun, A. A. (1); Jirawuthiworavong, Guy; Hsu, Andy; Lynch, Shannon; Heller, K. B.

CS (1) Department of Ophthalmology, Doheny Eye Institute, University of Southern California, Los Angeles, CA USA

SO IOVS, (March 15, 1999) Vol. 40, No. 4, pp. S189.
Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology Fort Lauderdale, Florida, USA May 9-14, 1999 Association for Research in Vision and Opthalmology .

DT Conference

LA English

L9 ANSWER 19 OF 36 CA COPYRIGHT 2001 ACS
AN 132:320745 CA
TI Induction of tumor necrosis factor-alpha immunoreactivity in rat retinal pigment epithelial cells ischemic insult
AU Ogino, Dai; Shioda, Seiji; Miyamoto, Keiichi; Seki, Tamotsu; Ueda, Toshihiko; Kiuchi, Yuji; Koide, Ryohei; Nakai, Yasumitsu
CS Department of Anatomy, Showa University School of Medicine, Tokyo, 142-8555, Japan
SO Showa Univ. J. Med. Sci. (1999), 11(2), 93-103
CODEN: SUMSEG; ISSN: 0915-6380
PB Showa Medical Association and Showa University
DT Journal
LA English
AB Retinal pigment epithelium (RPE) plays an important role in retinal function, and may contribute to retinal degeneration via expression of specific cytokines. The retina of a four-vessel occlusion rat model was used to investigate the localization of TNF-.alpha. following ischemia/reperfusion, to det. whether TNF-.alpha. expression may contribute to retinal degeneration. At the ultrastructural level, the 2-day RPE cells were irregular in shape, and showed increased phagocytosis of rod outer segments. Immunohistochem. demonstrated that ischemia-damaged RPE cells showed upregulation of N-methyl-D-aspartate receptor type 1 (NMDA-R1) and TNF-.alpha. immunoreactivity. However the first appearance of NMDA-R1 immunoreactivity preceded that of the TNF-.alpha. immunoreactivity. Both the NMDA-R1 and TNF-.alpha. immunoreactivities were decreased with time. To investigate the effect of glutamate on TNF-.alpha. expression, cultured rat RPE cells were treated with 1 mM glutamate, and TNF-.alpha. gene expression was examd. by RT-PCR. TNF-.alpha. mRNA expression was increased after the 4-day glutamate treatment. These results suggest that TNF-.alpha. is synthesized in RPE cells, and may play an important role in the development of retinal degeneration induced by ischemia/reperfusion insult at an early stage. Glutamate may induce TNF-.alpha. expression via NMDA-R1.
RE.CNT 34
RE
(1) Adamis, A; Biochem Biophys Res Commun 1993, V193, P631 CA
(3) Becquet, F; J Cell Physiol 1994, V159, P256 CA
(4) Beutler, B; Adv Immunol 1988, V42, P213 CA
(6) Campochiaro, P; Exp Eye Res 1989, V49, P217 CA
(7) Cheng, B; Neuron 1994, V12, P139 CA
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 20 OF 36 CA COPYRIGHT 2001 ACS
AN 128:192938 CA
TI Preparation of peptidyl compounds having MMP and TNF inhibitory activity
IN Baxter, Andrew Douglas; Montana, John Gary
PA Chiroscience Limited, UK
SO PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9806696	A1	19980219	WO 1997-GB2149	19970808

W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR,

GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9738578	A1	19980306	AU 1997-38578	19970808
ZA 9707100	A	19980811	ZA 1997-7100	19970808
EP 925281	A1	19990630	EP 1997-935682	19970808

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI

PRAI GB 1996-16643 19960808
WO 1997-GB2149 19970808

OS MARPAT 128:192938

AB Peptidyl compds. R3SCHR4XNR5CHRYNR1R2 [X = CO, CS; Y = CO, CS, SO, or SO2; R = substituted aryl, heteroaryl, aryl- or heteroarylalkyl; R1, R2 = H, alkyl; R3 = H, acyl; R4, R5 = H, (un)substituted alkyl, aryl, heteroaryl, or cycloalkyl] were prepd. for use as MMP and TNF inhibitors. Thus, (S)-[2-(acetylthio)-5-phthalimidopentanoyl]-(S)-2-naphthylalanine N-methylamide was prepd. via coupling of (S)-[(1,1-dimethylethoxy)carbonyl]-2-naphthylalanine N-methylamide with (S)-2-(acetylthio)-5-phthalimidopentanoic acid.

L9 ANSWER 21 OF 36 USPATFULL

AN 1998:65228 USPATFULL

TI Use of pentoxifylline and other tumor necrosis factor blockers for the treatment of aids-associated optic neuropathy and other central nervous system diseases

IN Sadun, Alfredo A., San Marino, CA, United States
Gill, Parkash S., Agoura Hills, CA, United States
Dugel, Pravin U., Alhambra, CA, United States
Madigan, Michele, Hurlstone Park, Australia

PA University of Southern California, Los Angeles, CA, United States (U.S. corporation)

PI US 5763446 19980609

AI US 1992-858129 19920326 (7)

DT Utility

EXNAM Primary Examiner: Lambkin, Deborah

LREP Pretty, Schroeder & Poplawski

CLMN Number of Claims: 18

ECL Exemplary Claim: 1

DRWN 2 Drawing Figure(s); 1 Drawing Page(s)

LN.CNT 622

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB In accordance with the present invention, methods are provided for the treatment of visual loss and other neurological dysfunctions in AIDS patients employing agents capable of blocking TNF expression in the central nervous system.

L9 ANSWER 22 OF 36 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 8

AN 1998:392476 BIOSIS

DN PREV199800392476

TI Neutralizing TNF-alpha activity modulates T-cell phenotype and function in experimental autoimmune uveoretinitis.

AU Dick, Andrew D. (1); Duncan, Linda; Hale, Geoff; Waldmann, Herman; Isaacs, John

CS (1) Dep. Ophthalmol., Univ. Aberdeen Med. Sch., Foresthill, Aberdeen AB25 2ZD UK

SO Journal of Autoimmunity, (June, 1998) Vol. 11, No. 3, pp. 255-264. ISSN: 0896-8411.

DT Article

LA English

AB **Inhibiting TNF**-alpha activity prevents tissue destruction without inhibiting **retinal** T cell infiltration in experimental autoimmune uveoretinitis (EAU) in Lewis rats. To further determine the role of TNF-alpha in autoinimune uveitis we characterized T

cells isolated from **retinae** after treatment with a **TNF** -alpha **antagonist**. **TNF**-alpha activity was neutralized in vivo with a p55 **TNF**-alpha **receptor**-Ig fusion protein (sTNFr-Ig), administered 8 and 10 days after induction of EAU with heterologous **retinal** antigens. **Retinal** T-cell phenotype expression was examined by flow cytometry with respect to OX22 status (CD45RBlow or CD45RBhigh),, activation (OX40 and CD25 expression) and rate of r-cell apoptosis (Annexin V+PI- expression). Lymphocyte reactivity was assessed by proliferation responses and cytokine production to retinal antigens. Despite greater than 40% of CD4+ T cells being activated at the height of disease, the proportion of OX22low expression was reduced and T cells exhibited reduced IFN-gamma and elevated IL-4 production. Retinal T cells maintained antigen-specific proliferation and demonstrated a low apoptotic rate. Althrough in both animal groups, comparable numbers of T cells were isolated, neutralizing TNF activity suppressed Th1 effector mechanisms protecting against target organ damage.

L9 ANSWER 23 OF 36 CA COPYRIGHT 2001 ACS
AN 129:329575 CA
TI The mRNA expression of cytokines and their receptors in cultured iris pigment epithelial cells: a comparison with retinal pigment epithelial cells
AU Kociok, Norbert; Heppekausen, Heike; Schraermeyer, Ulrich; Esser, Peter; Thumann, Gabriele; Grisanti, Salvatore; Heimann, Klaus
CS Department of Vitreoretinal Surgery, University Eye Hospital, University of Cologne, Cologne, D-50931, Germany
SO Exp. Eye Res. (1998), 67(2), 237-250
CODEN: EXERA6; ISSN: 0014-4835
PB Academic Press
DT Journal
LA English
AB It has been suggested that human iris pigment epithelial (IPE) cells isolated from iridectomized tissue could be used as autologous cells for transplantation into the subretinal space in diseases with dysfunctional retinal pigment epithelium (RPE). RPE cells synthesize a no. of cytokines and their receptors which are important for its proper function. Nearly nothing is known about the capacity of IPE to synthesize cytokines or responding to them. To compare the mRNA expression of 36 cytokines or their receptors in cultured adult IPE cells and RPE cells the authors used semi-quant. reverse transcription polymerase chain reactions (RT-PCR). Included were cytokines with known expression in RPE to get a broad basis for comparing IPE cells: basic fibroblast growth factor (bFGF or FGF-2), and one of its receptor (FGFR-1), epidermal growth factor (EGF), and its receptor EGF-R, transforming growth factor .beta. (TGF.beta.), and its type III receptor TGF.beta.-R3, the platelet-derived growth factors and receptors (PDGF A, PDGF B, PDGF-R.alpha., PDGF-R.beta.), tumor necrosis factor .alpha. (TNF.alpha.), and 2 receptors TNF-R1 and TNF-R2, insulin (INS) with receptor INS-R, insulin-like growth factors (IGF1, IGF2), and receptors (IGF1-R, IGF2-R), vascular endothelial growth factor (VEGF), and 2 receptors (VEGF-R1 or FLT-1 and VEGF-R2 or FLK-1), the receptor for VEGF-C: VEGF-R3 or FLK-4, interleukin 6 (IL6), and its receptor (IL6-R), nerve growth factor (NGF), interleukin 1.alpha. (IL1.alpha.), and a receptor (IL1-R). In addn., cytokines or their receptors not known to be expressed in RPE were included to widen the picture of cytokine gene expression in the eye: stem cell factor (SCF), its receptor (SCF-R), low-affinity nerve growth factor receptor p75 (p75NGF-R), ciliary neutrothropic factor (CNTF), and its receptor (CNTF-R), glycoprotein 130 interleukin 6 transducer gp130 (IL6-SD), leukemia inhibitory factor (LIF),

and its receptor (LIF-R). Semiquant. expression data were obtained using series of 5-fold dilns. of each cDNA and a fixed no. of PCR cycles. The expression of RPE 65, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), and .beta.2-microglobulin (B2MG) was used as a control for cellular origin, RNA quality, and PCR conditions. With the exception of insulin and tumor necrosis factor .alpha. all other cytokines analyzed and their receptors were expressed in both IPE and RPE cells, even though the levels varied. No qual. or quant. difference were obsd. in the mRNA expression level of 34 (94%) of the cytokines or receptors between IPE and RPE. In contrast, the mRNA expression level of vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor 2 [VEGF-RS (FLK-1)] was lower in IPE than in RPE cells. As an increased expression of VEGF in the RPE in maculae with age-related macular disease could be involved in its pathogenesis, a decreased expression of angiogenic growth factors in IPE cells could possibly be beneficial for the therapy of age-related maculopathy if indeed other tasks of non-functional RPE cells could be performed by IPE cells. The similarity of the mRNA expression pattern in 94% of the cytokines analyzed supports the assumption that IPE cells potentially can perform functions of RPE cells in the appropriate environment. (c) 1998 Academic Press.

L9 ANSWER 24 OF 36 USPATFULL
AN 97:73656 USPATFULL
TI Inhibition of tumor necrosis factor by retinoic acid
IN Aggarwal, Bharat B., Houston, TX, United States
PA Research Development Foundation, Carson City, NV, United States (U.S. corporation)
PI US 5658949 19970819
AI US 1994-346626 19941130 (8)
RLI Continuation-in-part of Ser. No. US 1993-61471, filed on 17 May 1993, now patented, Pat. No. US 5457129
DT Utility
EXNAM Primary Examiner: Weddington, Kevin E.
LREP Adler, Benjamin Aaron
CLMN Number of Claims: 15
ECL Exemplary Claim: 1
DRWN 19 Drawing Figure(s); 18 Drawing Page(s)
LN.CNT 953
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A novel method of inhibiting production of two important mediators of cellular function, tumor necrosis factor and nitric oxide, and treating a pathophysiological state characterized by an undesirable production or level of tumor necrosis factor or nitric acid. The methods of the present invention employ retinoic acid compounds. The most preferred retinoic acid is all-trans-retinoic acid. Also provided is a method of inhibiting tumor necrosis factor receptors using retinoic acid-like compounds.

L9 ANSWER 25 OF 36 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1997:288235 BIOSIS
DN PREV199799587438
TI Dysregulation of **TNF** and **TNF-receptor** production in proliferative diabetic **retinopathy**.
AU Limb, G. A. (1); Hollifield, R. (1); Chignell, A. H.; Shilling, J.; Goldsmith, C. S. (1); Rusell-Jones, D. L.; Dumonde, D. C. (1)
CS (1) Dep. Immunol., St. Thomas' Hosp, London UK
SO Investigative Ophthalmology & Visual Science, (1997) Vol. 38, No. 4 PART 1-2, pp. S695.
Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology, Parts 1-2 Fort Lauderdale, Florida, USA May 11-16, 1997

ISSN: 0146-0404.
DT Conference; Abstract
LA English

L9 ANSWER 26 OF 36 CA COPYRIGHT 2001 ACS
AN 125:115149 CA
TI Peptidyl compounds and their therapeutic use as inhibitors of metalloproteases
IN Montana, John; Baxter, Andrew Douglas; Owen, David Alan; Watson, Robert John; Phillipson, Neil
PA Chiroscience Limited, UK
SO PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9611209	A1	19960418	WO 1995-GB2362	19951005
	W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, TJ, TM, TT, UA, UG, UZ, VN				
	RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9536127	A1	19960502	AU 1995-36127	19951005
	AU 695796	B2	19980820		
	ZA 9508396	A	19961007	ZA 1995-8396	19951005
	EP 784629	A1	19970723	EP 1995-933489	19951005
	EP 784629	B1	19990428		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	BR 9509237	A	19971021	BR 1995-9237	19951005
	HU 77282	A2	19980330	HU 1997-2222	19951005
	JP 10507170	T2	19980714	JP 1995-512416	19951005
	CN 1193978	A	19980923	CN 1995-195544	19951005
	AT 179431	E	19990515	AT 1995-933489	19951005
	ES 2133807	T3	19990916	ES 1995-933489	19951005
	FI 9701412	A	19970404	FI 1997-1412	19970404
	NO 9701537	A	19970604	NO 1997-1537	19970404
PRAI	GB 1994-20057	A	19941005		
	GB 1995-4907	A	19950310		
	GB 1995-9431	A	19950510		
	WO 1995-GB2362	W	19951005		

OS MARPAT 125:115149
AB Title compds. I [R1 = alkyl, alkenyl, (hetero)aralkyl, (hetero)aryl, etc.;
R2 = H, alkyl; R3 = various substituents optionally linked via alkyl or alkenyl bridge; X = NR4R5; R4 = H or (un)substituted alkyl; R5 = H, alkyl;
or NR4R5 = pyrrolidino, piperidino, morpholino, etc.; R7 = H, acyl; R8 = substituted aryl, (un)substituted heteroaryl, etc.] and their salts, solvates, and hydrates are claimed. The compds. have utility as inhibitors of matrix metalloproteinases and TNF.alpha. (no data), and are useful for treatment of certain degenerative diseases and cancers. For example, reaction of 2,3-dibromopropionic acid with thiolacetic acid in aq. KOH gave AcSCH2CH(SAc)CO2H, which was coupled with H-Leu-Phe-NHMe using EDC and HOBt in THF to give title compd. AcSCH2CH(SAc)CO-Leu-Phe-NHMe. Examples include prepns. of approx. 80 I and 125 precursors. A variety of specific I are also claimed.

L9 ANSWER 27 OF 36 CA COPYRIGHT 2001 ACS
AN 125:245532 CA
TI Mechanisms of interferon-induced inhibition of Toxoplasma gondii replication in human retinal pigment epithelial cells
AU Nagineni, Chandrasekharam N.; Pardhasaradhi, Komanduri; Martins, Maria C.;

Detrick, Barbara; Hooks, John J.
CS Laboratory Immunology, National Institutes Health, Bethesda, MD, 20892, USA
SO Infect. Immun. (1996), 64(10), 4188-4196
CODEN: INFIBR; ISSN: 0019-9567
DT Journal
LA English
AB Inflammation assocd. with retinochoroiditis is a major complication of ocular toxoplasmosis in infants and immunocompetent individuals. Moreover, T. gondii-induced retinal disease causes serious complications in patients with AIDS and transplant patients. The retinal pigment epithelial (RPE) cell is an important regulatory cell within the retina and is one of the cells infected with T. gondii in vivo. The authors have developed a human RPE (HRPE) cell in vitro model system to evaluate T. gondii replication and the regulation of this replication by cytokines. T. gondii replication was quantitated by counting the foci of infection (plaque formation) and the nos. of tachyzoites released into the supernatant fluids. Pretreatment of cultures with recombinant human tumor necrosis factor .alpha., .alpha. interferon (IFN-.alpha.), IFN-.beta., or IFN-.gamma. for 24 h prior to inoculation inhibited T. gondii replication in a dose-dependent manner. Of these cytokines, IFN-.gamma. was the most potent, and T. gondii replication was completely inhibited at a concn. of 100 U/mL. The anti-toxoplasmic activity of IFN-.gamma. was blocked by monoclonal antibody to IFN-.gamma.. Treatment of the cultures with IFN-.gamma. from day 1 or 2 postinoculation with T. gondii also offered protection against the parasite. The anti-toxoplasmic activity of tumor necrosis factor .alpha. or IFN-.alpha., -.beta., or -.gamma. in these cultures was independent of the nitric oxide (NO) pathway, since NO prodn. was not found in HRPE cells treated with these cytokines. However, addn. of tryptophan to IFN-.gamma.-treated cells reversed the inhibitory effects of IFN-.gamma., suggesting that IFN-.gamma. acts by depleting cellular tryptophan. This effect was further confirmed by reverse transcription-PCR and Northern (RNA) blot anal., which indicated induction of indoleamine 2,3-dioxygenase (IDO), an enzyme that converts tryptophan to kynurenine. Thus, interferons inhibited T. gondii replication in HRPE by NO-independent but IDO-dependent mechanisms. This in vitro model of T. gondii replication in HRPE may be useful in evaluating the effects of cytokines and drugs on T. gondii replication within the retina.

L9 ANSWER 28 OF 36 DRUGU COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 1996-25532 DRUGU P V
TI CD23-mediated nitric oxide synthase pathway induction in human keratinocytes is inhibited by retinoic acid derivatives.
AU Becherel P A; Le Goff L; Ktorza S; Chosidow O; Frances C; Issaly F; Mencia Huerta J M; Debre P; Mossalayi M D; Arock M
CS Inst.Henri-Beaufour
LO Les Ulis; Paris, Fr.
SO J.Invest.Dermatol. (106, No. 6, 1182-86, 1996) 6 Fig. 35 Ref.
CODEN: JIDEAE ISSN: 0022-202X
AV Department of Immunology (CNRS URA 625), Faculte de Medecine de la Pitie-Salpetriere, Room 510, 91 Bd de 1'Hopital, 75013, Paris, France. (M.A.).
LA English
DT Journal
FA AB; LA; CT
FS Literature
AB This study investigated the effects of retinoic acid (RA) derivatives on the production of nitric oxide (NO) by human keratinocytes activated with

IgE/anti-IgE or anti-CD23 monoclonal antibody. 13-cis RA (isotretinoin) and all-trans RA (tretinoin) (both Sigma-Chem.) reduced the production of nitrites by IgE-activated keratinocytes by 80%. The RA derivatives also reduced the production of tumor necrosis factor (TNF)-alpha by these cells by 70%. Retinol and retinaldehyde (both Sigma-Chem.) were less active. The level of inducible NO synthase activity in activated keratinocytes was decreased upon treatment with RA derivatives. RA derivatives down-regulated TNF-alpha release and the NO-transduction pathway through the inhibition of inducible NO synthase transcription. The results may clarify the mechanism of the antiinflammatory effect of RA derivatives in skin diseases.

L9 ANSWER 29 OF 36 CA COPYRIGHT 2001 ACS DUPLICATE 9
AN 125:8259 CA
TI **Inhibition** of **tumor necrosis factor** activity minimizes target organ damage in experimental autoimmune uveoretinitis despite quantitatively normal activated T cell traffic to the **retina**
AU Dick, Andrew D.; McMenamin, Paul G.; Korner, Heinrich; Scallon, Bernard J.; Ghrayeb, John; Forrester, John V.; Sedgwick, Jonathon D.
CS Centenary Inst. Cancer Med. Cell Biol., Sydney, 2050, Australia
SO Eur. J. Immunol. (1996), 26(5), 1018-1025
CODEN: EJIMAF; ISSN: 0014-2980
DT Journal
LA English
AB Recent studies demonstrated that administration of a p55-tumor necrosis factor (TNF) receptor IgG-fusion protein (TNFR-IgG) prevented the clin. onset of exptl. autoimmune encephalomyelitis but did not alter the no. or tissue distribution of autoantigen-specific CD4+ effector T cells which trafficked into the central nervous system. To det. whether specific target tissues of autoimmune damage remain intact after TNFR-IgG treatment despite the presence of inflammatory cells within the tissues, we examd. rats with exptl. autoimmune uveoretinitis (EAU), as in this model, the main target of autoreactive CD4+ T cells, the retinal rod outer segments (ROS), can be examd. readily by light microscopy. As judged by direct ophthalmoscopy, the onset of inflammation in the anterior chamber of the eye in EAU following administration of TNFR-IgG was delayed by 6 days compared to untreated controls, but the magnitude of the response was only slightly less than controls. Histol. examn. of the retinae and direct assessment of retinal inflammation revealed a disproportionate sparing of ROS in the TNFR-IgG-treated animals despite a level of retinal inflammation not substantially less than controls in which ROS damage was marked. Anal. of retinal leukocytes by immunofluorescence microscopy and flow cytometry indicated that approx. equal nos. of CD4+.alpha..beta.TCR+ lymphocytes were present in treated and control retinae, more than 30% of CD4+ cells in both exptl. groups expressed the CD25 or MRC OX40 activation markers and most cells, which would include the CD4+ T lymphocytes, were activated as evidenced by MHC class II expression. Fewer activated macrophages and granulocytes were present in the treated retinae, possibly reflecting the lower level of tissue damage and subsequent accumulation of these inflammatory cells. The results demonstrate directly that a tissue specifically targeted for autoimmune destruction can be protected despite the influx of fully activated CD4+ T cells.

L9 ANSWER 30 OF 36 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 10
AN 1996:195952 BIOSIS
DN PREV199698752081
TI Induction of intercellular adhesion molecule-1 by tumor necrosis factor-alpha through the 55-kDa receptor is dependent on protein kinase C

in human retinal pigment epithelial cells.
AU Sippy, Brian D.; Hofman, Florence M.; Wright, Albion D.; Wang, Jin Lin; Gopalakrishna, Rayudu; Gundimeda, Usha; He, Shikun; Ryan, Stephen J.; Hinton, David R.
CS Dep. Pathol., Univ. Southern California Sch. Med. HMR 209, 2011 Zonal Avenue, Los Angeles, CA 90033 USA
SO Investigative Ophthalmology & Visual Science, (1996) Vol. 37, No. 4, pp. 597-606.
ISSN: 0146-0404.
DT Article
LA English
AB Purpose: To determine second messenger signaling pathways associated with tumor necrosis factor-alpha (TNF)-mediated induction of intercellular adhesion molecule (ICAM)-1 expression on human **retinal** pigment epithelial (HRPE) cells, a cell type known to express only the 55-kDa **TNF receptor** (TNFR p55). Methods: SV-40-immortalized HRPE (SVRPE) cells were exposed to TNF with and without pretreatment with the protein kinase C (PKC) inhibitor calphostin C or the protein kinase A (PKA) inhibitor H8. SV40-immortalized HRPE cells also were treated with the PKC activator phorbol 12-myristate 13-acetate (PMA) or with the PKA activators forskolin plus 3-isobutyl-1-methyl-xanthine or dibutyryl cyclic adenosine monophosphate (cAMP) alone. Membrane fractions from untreated and treated SVRPE cells were assayed for PKC activity, and whole cell lysates were assayed for cAMP accumulation and PKA activity. Flow cytometry was performed on SVRPE cells using a monoclonal antibody specific to ICAM-1. Results: Activation of TNFR p55 on SVRPE cells with TNF resulted in a rapid increase of PKC activity at 1 minute, with a subsequent downregulation to baseline. There was no increase in intracellular cAMP accumulation or PKA activity within the first 10 minutes; however, both increased within 30 minutes and returned to baseline within 1 hour. SV40-immortalized HRPE cells treated with TNF for 1 hour showed maximal induction of ICAM-1 expression at 18 hours. ICAM-1 induction by TNF treatment was inhibited by calphostin C pretreatment and not by H8 pretreatment. Protein kinase C activation with PMA for 3 hours was sufficient to induce ICAM-1 on SVRPE cells at 18 hours, whereas treatment with the PKA activators forskolin or dibutyryl cAMP did not induce ICAM-1 expression. Conclusion: Tumor necrosis factor sequentially activates the PKC and PKA pathways in SVRPE cells by way of the TNFR p55. The PKC pathway is necessary for TNF-mediated ICAM-1 upregulation, and specific activation of the PKC pathway with PMA is sufficient to induce ICAM-1 on these cells. SV40-immortalized HRPE cells may serve as a model in which to study further the functional signaling pathways associated with TNFR p55.

L9 ANSWER 31 OF 36 CA COPYRIGHT 2001 ACS DUPLICATE 11
AN 125:219260 CA
TI Soluble **tumor necrosis factor receptors** are present in human vitreous and shed by **retinal** pigment epithelial cells
AU Sippy, Brian D.; Hofman, Florence M.; Wright, Albion D.; He, Shikun; Ryan, Stephen J.; Hinton, David R.
CS Departments of Pathology, Ophthalmology, Neurology and Neurological Surg., Univ. of Southern California School of Medicine, Los Angeles, CA, USA
SO Exp. Eye Res. (1996), 63(3), 311-317
CODEN: EXERA6; ISSN: 0014-4835
DT Journal
LA English
AB Tumor necrosis factor-alpha (TNF) has been implicated in the pathogenesis of several retinal diseases. Sol. forms of the TNF receptors, p55 (55 kDa) and p75 (75 kDa), have recently been identified in biol. fluids and may regulate TNF activity. The potential biol. significance of these receptors for the human retina was examd. by detg. their presence in human

vitreous and their release from eye cup explants in which the retina has been removed leaving an intact retinal pigment epithelium (HRPE). Normal human vitreous and conditioned medium from eye-cup HRPE explants demonstrated the presence of sol. p55 and p75. Sol. p55 was significantly more abundant than p75 in all vitreous samples ($P < 0.03$). Conditioned medium from eye-cup HRPE explants contained significantly more sol. p55 than p75 ($P < 0.00002$). ELISA showed the presence of sol. p55, and not p75, in conditioned medium from primary cultured HRPE cells. Activation of the protein kinase C pathway in these cells with the phorbol ester PMA significantly increased the release of sol. p55 ($P < 0.001$); whereas, pharmacol. inhibition of protein kinase C with calphostin-C significantly decreased the shedding of p55 ($P < 0.001$). The results indicate that primary cultured HRPE cells shed p55 and regulate this shedding in part through the protein kinase C pathway. The presence of sol. TNF receptors within normal human vitreous and within conditioned medium from the eye-cup HRPE explant model suggests that these sol. receptors may have a biol. function in the eye.

L9 ANSWER 32 OF 36 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 12
AN 1996:473995 BIOSIS
DN PREV199699203551
TI Induction of cell death by endogenous nerve growth factor through its p75 receptor.
AU Frade, Jose Maria; Rodriguez-Tebar, Alfredo; Barde, Yves-Alain (1)
CS (1) Max-Planck-Inst. Psychiatry, Dep. Neurobiochem., 82152 Planegg-Martinsried Germany
SO Nature (London), (1996) Vol. 383, No. 6596, pp. 166-168. ISSN: 0028-0836.
DT Article
LA English
AB During development, neuronal survival is regulated by the limited availability of neurotrophins, which are proteins of the nerve growth factor (NGF) family. Activation of specific irk tyrosine kinase receptors by the neurotrophins blocks programmed cell death. The trkA-specific ligand NGF has also been shown to activate the non-tyrosine kinase receptor p75, a member of the **tumour necrosis factor** (**TNF**) **receptor** and Fas (APO-1/CD95) family. Here we report that, early in development, endogenous NGF causes the death of **retinal** neurons that express p75 but not trkA. These results indicate that, as with cells of the immune system, the death of neurons in the central nervous system can also be induced by ligands, and that the effect of NGF on cell fate depends on the type of receptor expressed by developing neurons.

L9 ANSWER 33 OF 36 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1996:138639 BIOSIS
DN PREV199698710774
TI Soluble **tumor necrosis factor receptors** are present in human vitreous and shed by **retinal** pigment epithelial cells.
AU Sippy, B. D. (1); Hofman, F. M. (1); Wright, A. D. (1); He, S. (1); Ryan, S. J.; Hinton, D. R. (1)
CS (1) Dep. Pathol., Univ. Southern California Sch. Med., Los Angeles, CA USA
SO Journal of Investigative Medicine, (1996) Vol. 44, No. 1, pp. 117A. Meeting Info.: Meeting of the American Federation for Clinical Research, Western Region Carmel, California, USA February 14-17, 1996 ISSN: 1081-5589.
DT Conference
LA English

L9 ANSWER 34 OF 36 USPATFULL
AN 95:90553 USPATFULL

TI Inhibition of nitric oxide production by retinoic acid
IN Aggarwal, Bharat B., Houston, TX, United States
Mehta, Kapil, Houston, TX, United States
PA Research Development Foundation, Carson City, NV, United States (U.S. corporation)
PI US 5457129 19951010
AI US 1993-61471 19930517 (8)
DT Utility
EXNAM Primary Examiner: Kenley, III, Raymond; Assistant Examiner: Weddington, K. E.
LREP Adler, Benjamin Aaron
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN 9 Drawing Figure(s); 6 Drawing Page(s)
LN.CNT 535
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A novel method of inhibiting production of two important mediators of cellular function, tumor necrosis factor and nitric oxide, and treating a pathophysiological state characterized by an undesirable production or
level of tumor necrosis factor or nitric acid. The methods of the present invention employ retinoic acid compounds. The most preferred retinoic acid is all-trans-retinoic acid.

L9 ANSWER 35 OF 36 CA COPYRIGHT 2001 ACS
AN 119:262532 CA
TI Use of tumor necrosis factor blockers for the treatment of AIDS-associated
optic neuropathy and other central nervous system diseases
IN Sadun, Alfredo A.; Gill, Parkash S.; Dugel, Pravin U.; Madigan, Michele
PA University of Southern California, USA
SO PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9318770	A1	19930930	WO 1993-US2704	19930324
	W: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML				
	US 5763446	A	19980609	US 1992-858129	19920326
	AU 9348085	A1	19931021	AU 1993-48085	19930324
PRAI	US 1992-858129		19920326		
	WO 1993-US2704		19930324		

AB AIDS-assocd. central nervous system diseases such as optic neuropathy is treated with administration of blockers of tumor necrosis factor (TNF), e.g. pentoxifylline. These agents are capable of blocking expression of TNF, or neutralizing TNF in the central nervous system. Time and dose dependent axonal loss in rabbit optic nerves following injection of 1x102 and 1x104 U/mL TNF after 1, 4, 8, 12, and 24 wks were shown.

L9 ANSWER 36 OF 36 BIOSIS COPYRIGHT 2001 BIOSIS
AN 1988:301863 BIOSIS
DN BR35:18687
TI CHARACTERIZATION OF **TUMOR NECROSIS FACTOR**'S **TNF INHIBITORY** EFFECT ON THE PROLIFERATION AND PERMEABILITY FUNCTION OF **RETINAL** CAPILLARY ENDOTHELIAL CELLS.
AU BERMAN A; KOPOLOVIC K; BROWNLEE M; KING G L
CS JOSLIN DIABETES CENT., DEP. MED., HARV. MED. SCH., BOSTON, MASS., USA.
SO ANNUAL SPRING MEETING OF THE ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY, SARASOTA, FLORIDA, USA, MAY 1-6, 1988. INVEST OPHTHALMOL